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## When helping the minority of patients may hurt the majority: The case for DPD phenotyping and 5-fluorouracil therapeutic drug monitoring

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1 **When helping the minority of patients may hurt the majority: the case for DPD**  
2 **phenotyping and 5-fluorouracil therapeutic drug monitoring.**

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22 **Dear Editor,**

23 5-fluorouracil (5-FU) is still the backbone in some cancer treatments particularly in digestive cancers.  
24 The drug is associated with potential severe adverse events leading in some cases in substantial  
25 morbidity and mortality. As the drug is essentially catabolized through an enzymatic process mediated  
26 by dihydropyrimidine deshydrogenase (DPD), DPD deficiency is thought to be the main mechanism  
27 leading to 5-FU accumulation and toxicity [1]. Identifying patients with DPD deficiency and notably  
28 patients with complete deficiency, is then a relevant approach to limit the risk of severe adverse event.  
29 Recently, the European Agency for Medicine has therefore recommended DPD deficiency screening  
30 prior a treatment with fluorouracil or one of these derivatives [2].

31 The rate for complete DPD deficiency in Caucasian population is estimated to up to 0.5% to 1%, while  
32 up to 9% of patients may have some kind of partial enzymatic deficiency [2]. Thus, considerable effort  
33 should be undertaken to recognize these patients before any initiation of 5-FU treatments. Genotyping  
34 approach allows identifying patients carriers of one the four most common allelic variants associated  
35 with a loss or a decrease of function of DPD. Although frequencies of the variants of interest are low,  
36 these pharmacogenetics tests could be useful in some cases to explain an enzymatic deficiency.  
37 However, on a large cohort, genotyping was shown to be poorly predictive of DPD deficiency [3].  
38 Actually, the phenotyping approach appears more appropriate to screen DPD deficiency. Because  
39 DPD catabolized uracil into its metabolite, dihydro-uracil, measuring uracil plasma level before any  
40 treatment initiation is the recommended phenotyping method aiming at preventing the drug toxicity at  
41 the first treatment cycle. In France, a concentration threshold of 16 ng/mL of uracil in plasma is  
42 proposed to categorize patients with potential partial DPD deficiency while a concentration above 150  
43 ng/mL prohibits any 5-FU treatment. For patients with uracil plasma level between 16 and 150 ng/mL,  
44 caution is required and the treatment dosage may be decreased to prevent drug toxicity [4,5]. This  
45 situation can be frequent since a recent study reported that 15 % of the patient of its cohort (n= 526)  
46 had uracil concentration within this range [6]. As a result, an important part of patients treated with 5-  
47 FU receives a reduced drug dosage.

48 However, it is known that there is a wide inter-individual variability of 5-FU exposure and that in  
49 digestive cancer, most of patients treated with 5-FU are underexposed to the drug even when treated  
50 with the standard regimen [7]. At usual dosage, around 50% of patients displays low drug exposure,  
51 when targeting a 5-FU area under the curve of drug concentrations (AUC) exposure of 20-30 ng.h/mL  
52 [7]. Consequently, the risk for low 5-FU exposure might be further increased due to the DPD  
53 phenotyping. It is of utmost importance since 5-FU exposure has been related to overall response rate  
54 in a randomized multicenter study conducted in metastatic colorectal cancer patients [8].

55 The aim of the present study was to assess the relationship between DPD phenotype and the 5-FU  
56 exposure during the first treatment cycle.

57 We included in the analysis patients treated for digestive or head and neck cancers in Rennes  
58 University Hospital and the Eugène Marquis Anticancer Center, with a regimen including continuous  
59 infusion of 5FU. Data were collected from April 2019 to June 2020 based on the routine follow-up of  
60 patients. The study was approved by the local ethical committee (authorization n° 20.98). DPD  
61 phenotyping was performed by measuring uracil concentration in plasma (uracilemia) before the  
62 chemotherapy according to national recommendations [4,5]. Uracilemia was measured using a  
63 validated high performance liquid chromatography tandem mass spectrometry method in the Rennes  
64 University Hospital laboratory. At the first 5-FU cycle (C1), concentration of 5-FU in plasma was  
65 determined in a sample collected during the infusion (between 18h after the start of the infusion and  
66 4h before the end) in order to measure 5-FU at steady state according to Adjei *et al.* [9]. Because 5-FU  
67 is very unstable *ex-vivo* in the blood sample (due to the remaining DPD metabolism), a DPD inhibitor  
68 was added in the sample immediately after blood withdrawal. Then, 5-FU was quantified by an  
69 immunoassay [10]. Genotype of *DPYD* (the gene encoding the DPD) was available when it was  
70 requested by clinicians for patients who consented to this analysis. The following demographic and  
71 therapeutic parameters were collected routinely and prospectively: age, sex, weight, chemotherapy  
72 regimen, dose of 5-FU continuous infusion at C1.

73 A total of 42 patients were enrolled in the study. Their characteristics are reported in Table 1. No  
74 linear correlation was found between uracil concentration and 5-FU clearance or 5-FU exposure at C1  
75 (Figure 1). Furthermore, sixty-six percent of patients had 5-FU AUC below the therapeutic threshold  
76 of 20-30 ng.h/mL at C1. The rate of underexposed patients according to DPD status revealed that 5-  
77 FU underexposure trended to be more frequent in patient with partial DPD deficiency than in patients  
78 without DPD deficiency (75% vs 57% in uracilemia  $\geq 16$  ng/mL and  $< 16$  ng/mL respectively.  
79  $p=0.28$ , F-test) (Figure 2). Besides, according to the recommendations, all patients with pre-  
80 therapeutic uracilemia  $\geq 16$  ng/mL received a decreased dose of 5-FU at C1 (of at least -20%)  
81 compared to the protocol-specified dose. In patients without DPD deficiency, only 13% received a  
82 decreased dose at C1.

83 Systematic screening of DPD deficiency before any 5-FU (or other fluoropyrimidine) based treatment  
84 is crucial to prevent rare but early and highly severe 5-FU related toxicities. In France, this screening  
85 is now mandatory by the phenotyping approach based on uracilemia. Indeed, several studies have  
86 shown that uracilemia was a surrogate marker of 5-FU early toxicity [5]. The range of uracil  
87 concentrations associated with partial DPD deficiency is wild (16-150 ng/mL) and to date, no  
88 algorithm is available to choose the appropriate starting 5-FU dose based on uracilemia. Thus, it is  
89 challenging for clinicians and laboratory scientists to accurately determine the magnitude of the dose  
90 decrease to apply at C1. Usually, an empirical reduction of 20 to 30 % of the standard dose is applied  
91 for patients with moderate increase of uracilemia (16-40 ng/mL). In the present work we reported that  
92 this strategy tended to worsen the proportion of patients underexposed to 5-FU especially when  
93 uracilemia was slightly high as the majority of DPD deficient patients from our cohort. Despite  
94 differences were not statistically significant, likely due to the small sample size of our cohort, we  
95 wanted to alert readers on the potential risk of 5-FU underexposure meaning that more than never  
96 patients would benefit of 5-FU plasma concentration measurement as early as C1. The recent work  
97 from Chamorey *et al.* supports this statement, since this team evidenced that patients with high DPD  
98 activity (so likely low 5-FU plasma exposure) had poorer overall survival, progression free survival  
99 and response rate [11]. We admit that a limit of our work is the lack of data regarding patient toxicity

100 at C1. Guidelines clearly state that if a dose reduction was applied at C1, the dose should be increased  
101 at the next cycle when the first cycle was well tolerated, in order to maximise the treatment efficacy  
102 [5]. However, it can be challenging and take several cycles to find the patient's optimal 5-FU dose in  
103 this context. It appears much more efficient to monitor 5-FU concentration in plasma at C1 and at the  
104 next cycle if needed, since a validated dosage algorithm is available to safely choose dose the increase  
105 leading to 5-FU therapeutic exposure [10]. Thus, therapeutic drug monitoring of 5-FU is a time saving  
106 approach, easy to implement in clinical practice and strongly recommended to optimized and  
107 individualized 5-FU dosages [7]. Hence, to our point of view, the required DPD phenotyping approach  
108 aiming at preventing toxicities in patients with deep DPD deficiency should be systematically  
109 associated with 5-FU exposure evaluation using therapeutic drug monitoring, otherwise it could be  
110 detrimental for the treatment efficacy in a significant proportion of patients who had no toxicity  
111 following the first cycle of 5-FU based chemotherapy.

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155 **Figures legends:**

156

157 **Figure 1: Relationship between uracilemia and 5-FU clearance (A) or exposure (B) at first cycle.**

158 ***p*: p-value pearson correlation test. Clearance was calculated as follow : Dose 5FU continuous**

159 **infusion (mg) / AUC 5-FU (mg.h/mL).**

160 5-FU: 5-fluorouracil; AUC: area under the curve of drug concentrations

161 **Figure 2: Percentage of patients with 5-FU AUC values below, within or above the therapeutic**

162 **range at first cycle depending on the DPD activity status**

163 5-FU: 5-fluorouracil; AUC: area under the curve of drug concentration; DPD: dihydropyrimidine

164 deshydrogenase

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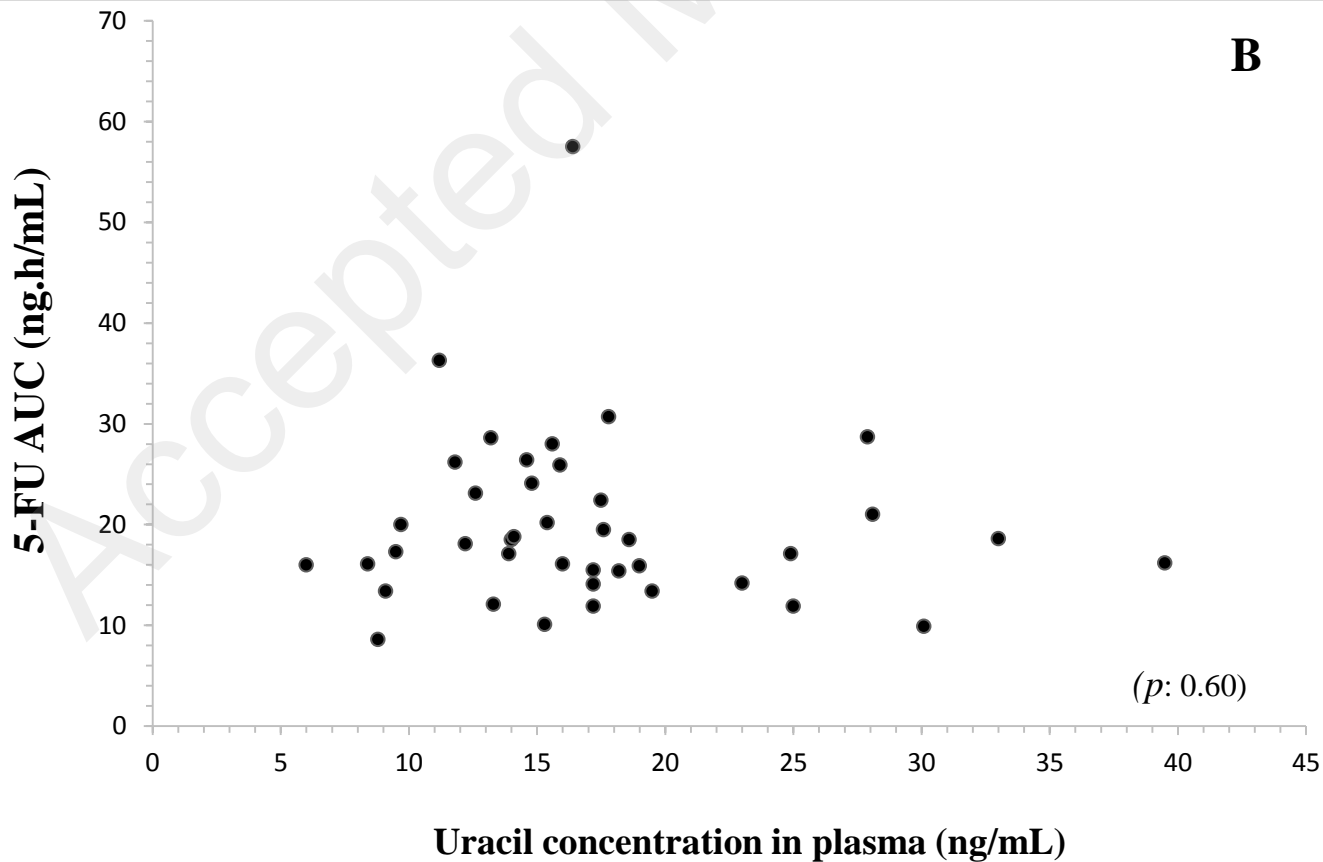
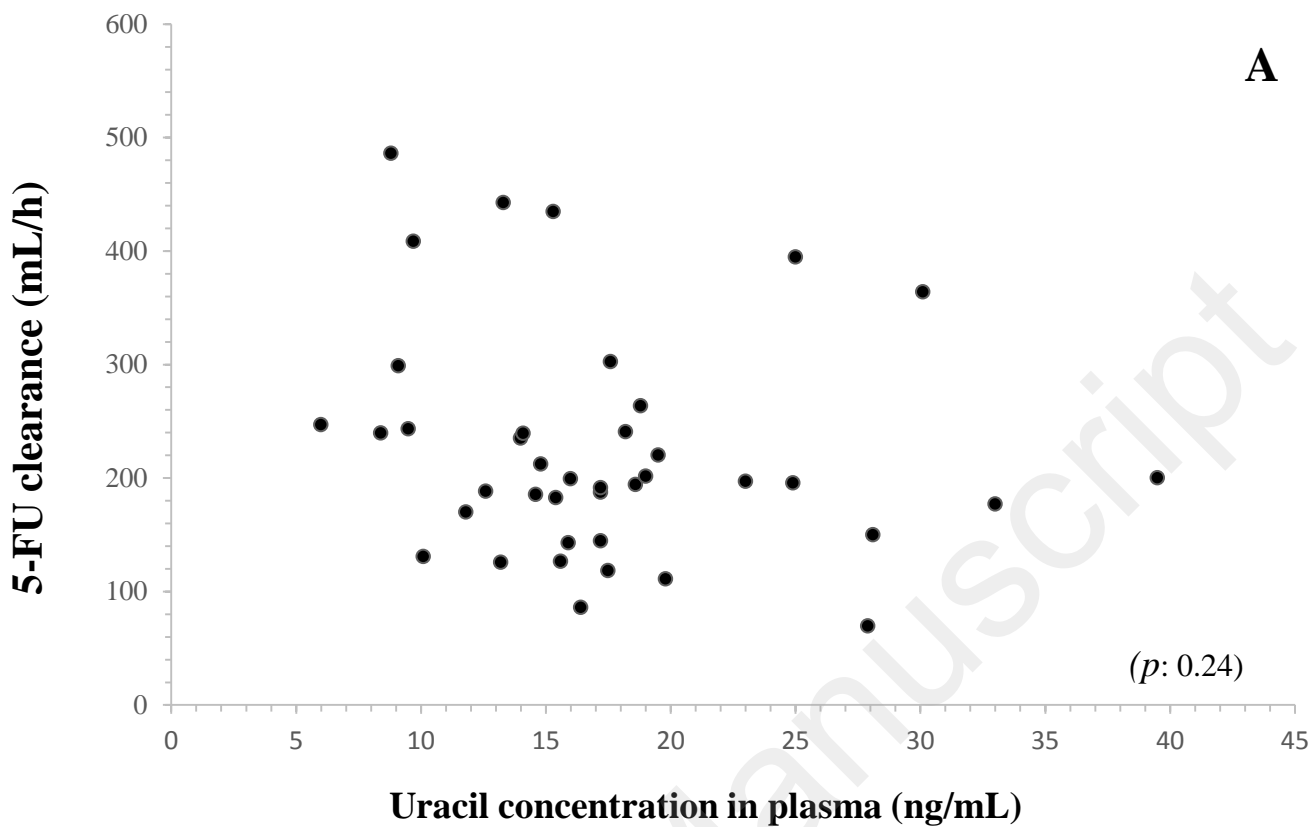
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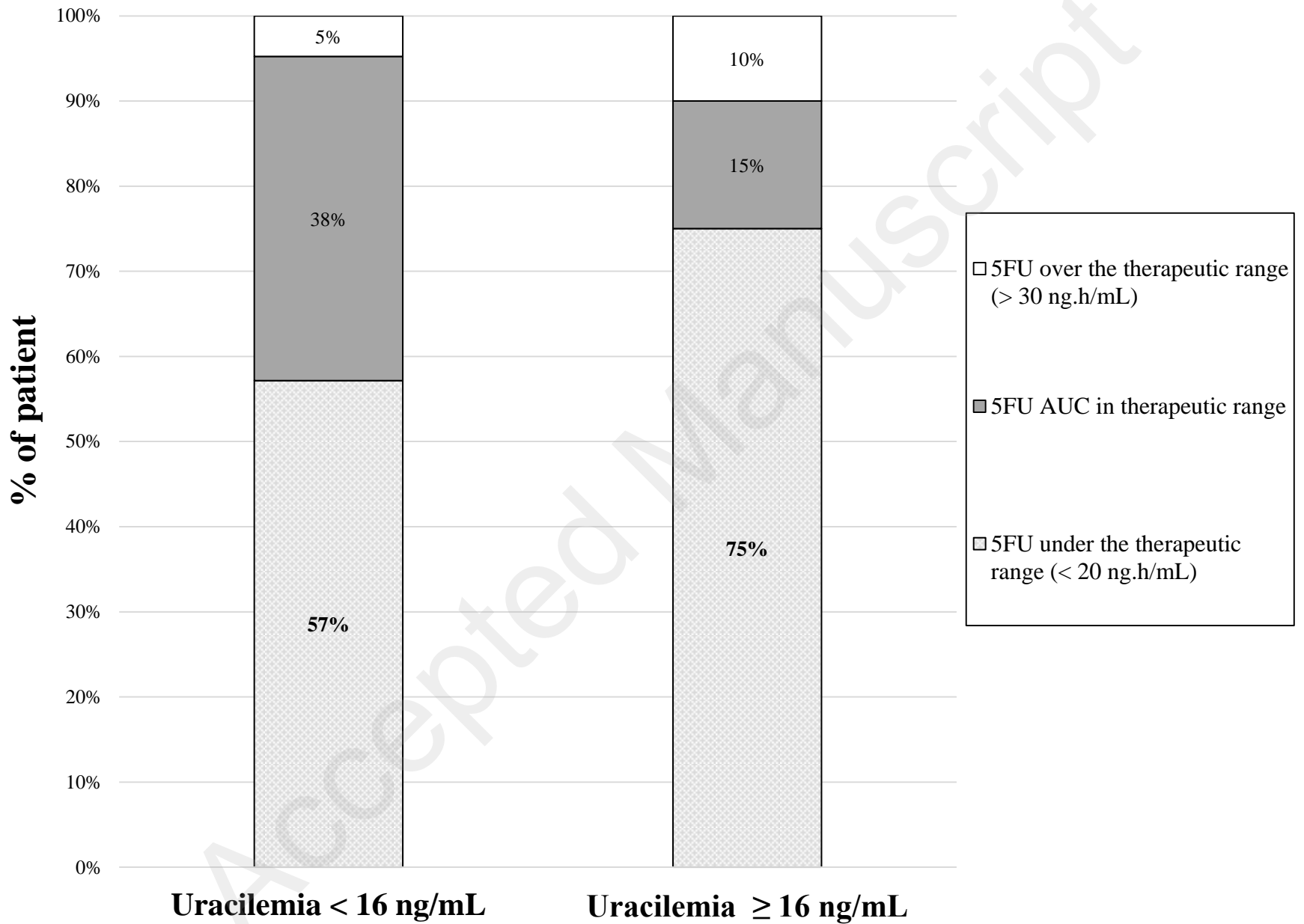
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**Table 1: Patients characteristics (n=42)**

<b>Age (years) (mean±SD)</b>		66 ± 9.6
<b>Sex</b>		
	M (n)	31
	W (n)	11
<b>Weight (kg) (mean±SD)</b>		68.3 ± 14.5
<b>Indications</b>		
	Digestive cancer (n)	39
	Head and neck cancer (n)	3
<b>5-FU protocol (n)</b>		
	carboplatin-5FU	3
	FOLFIRI	1
	FOLFIRINOX	10
	FOLFOX	26
	LV5FU2	1
	DCF	1
<b>DPYD Genotype<sup>a</sup></b>		
	No variant (n)	18
	hapB3, c.1129-5923C>G (heterozygous) (n)	2
<b>5-FU dose at C1 (mean (CV))</b>	mg/m <sup>2</sup>	2094 (22%)
	mg	3768 mg (24%)
<b>5-FU exposure (AUC in ng.h/mL) (mean (CV))</b>		19.3 (43%)
<b>Uracile</b>		
	Mean (ng/mL)	17.5
	Min-max (ng/mL)	6-39.5
	No DPD deficiency (%) (Uracilemia <16ng/mL)	51
	DPD deficiency (%) (Uracilemia ≥16ng/mL)	49

5-FU : 5 fluorouracile ; C1: first cycle; FOLFIRI (leucovorin + 5FU + irinotecan); FOLFIRINOX (leucovorin + 5FU + irinotecan + oxaliplatin); FOLFOX (leucovorin + 5FU + oxaliplatin); LV5FU2 (leucovorin + 5FU) ; DCF (docetaxel + cisplatin + 5FU) ; M: men ; W: women ; AUC: area under the curve ; SD: standard deviation ; CV: coefficient of variation; DPYD: gene encoding dihydropyrimidine deshydrogenase

<sup>a</sup>The four variants of *DPYD* included in the analysis were : rs55886062 (\*13, no function allele), rs3918290(\*2, no function allele), rs67376798 (decrease function allele), rs75017182 (HapB3, decrease function allele)